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TITLE: Deficient BIM Expression as a Mechanism of Intrinsic and Acquired Resistance to Targeted Therapies in EGFR-Mutant and ALK-Positive Lung Cancers

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13. SUPPLEMENTARY NOTES

14. ABSTRACT
This project has made very good progress. We have now unveiled an even larger role for defective apoptosis in the emergence of resistance. We have been very successful in our ability to generate cell lines derived from patient biopsies both before treatment and at the time of resistance. We are now using these patient-derived cell lines to assess BIM levels and apoptotic response to next-generation inhibitors. The capacity to develop cell lines from patient biopsies was published in December, 2014 in *Science*. We have used these models to develop effective combinations to overcome the defect in apoptosis which has led to a CTEP-sponsored clinical trial combining AZD9291 and ABT-263. Our research has expanded beyond just assessing BIM, and is also focusing on the role of a diminished apoptotic response as clones develop resistance to targeted therapies. Although BIM is one such mechanism, it is not the only one. This research has uncovered a novel, unexpected connection between EMT, low BIM, and resistance to targeted therapies. Two manuscripts (one under review at *Nature Communications* and one to be submitted) have been written this year describing our findings.

15. SUBJECT TERMS
BIM, apoptosis, targeted therapy, BCL-XL, kinase, EGFR, ALK, lung cancer

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1. INTRODUCTION: Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

In lung cancers that have oncogene-addiction to a specific kinase, inhibition of that kinase often leads to cell growth arrest and apoptosis. For example, *EGFR* mutant and *EML4-ALK* lung cancers have been proven highly sensitive to the corresponding specific tyrosine kinase inhibitors (TKIs). Although cancers with these genetic abnormalities often respond to the appropriate targeted therapy, there is marked heterogeneity in degree of clinical benefit. We hypothesized that that some cancers are poised to undergo apoptosis following treatment, whereas others are not; and expression of the critical pro-apoptotic protein BIM in pre-treatment biopsies may distinguish patients who have impressive, durable responses from those who have weak, transient responses. We originally aimed to assess *EGFR* mutant and *EML4-ALK* lung cancer specimens to determine if low basal BIM expression predicts a poorer clinical outcome to TKIs.

Since the inception of this research program, our findings have led us to appreciate the fundamental importance of diminished apoptosis for the evolution of resistance to targeted therapies. We have now determined that *EGFR* mutant cancers will have different apoptotic responses to 2nd and 3rd line targeted therapies depending on "how" the cancer became resistant (please see Figure 1 below for a description of the different models for how cancers become resistant). These fundamental findings have been put together for publication and are now under review at *Nature Medicine* and are the basis for a new clinical trial that is about to begin (ABT-263 + AZD9291 in *EGFR* mutant lung cancers (clinicaltrials.gov NCT02520778)). We have aligned the aims of this proposal with this promising avenue of investigation.

We have studied this process in detail in *EGFR* mutant cancers that develop the T790M resistance mutation under the selective pressure of gefitinib. We now have 2 models for how cancers become resistant to targeted therapies:

1) Pre-existing model: In this model, cells with acquired resistance to EGFR inhibitors exist prior to treatment and are simply selected by treatment.

2) Persister-evolution model: In this model, cancer cells that initially survive therapy are selected by drug treatment. **These cells do not undergo apoptosis.** During weeks and months of therapy, these cells can develop mutations and become fully resistant. However, the tumors that evolve from these drug tolerant cells continue to have an apoptotic defect.
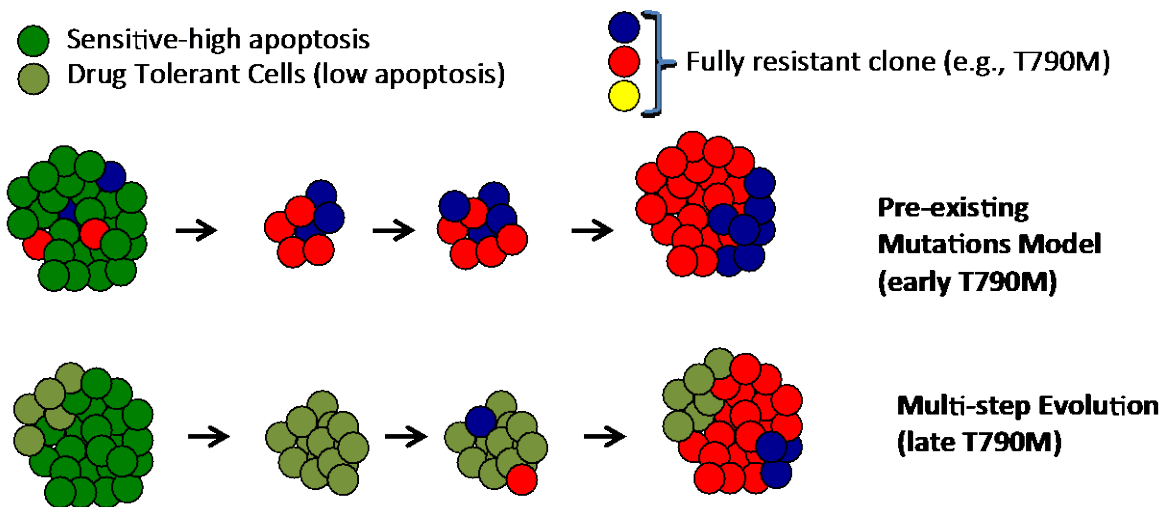
Figure 1. Two models of the development of acquired resistance to EGFR inhibitors

We continue to leverage our robust repeat biopsy program that routinely biopsies patients upon the development of resistance. This effort is led by my co-PI, Lecia Sequist. We are now able to cultivate cell cultures from these resistant cancers which allow us to not only to measure BIM levels, but also to functionally determine if these cancers have an impaired apoptotic response to next-generation inhibitors.

2.KEYWORDS: Provide a brief list of keywords (limit to 20 words).

BIM, apoptosis, targeted therapy, BCL-XL, kinase, EGFR, ALK, lung cancer

3.OVERALL PROJECT SUMMARY: This project has made very good progress. As noted above, we have now unveiled an even larger role for defective apoptosis in the emergence of resistance. We are now using patient-derived cell lines to assess BIM levels and apoptotic response to next-generation inhibitors. The capacity to develop cell lines from patient biopsies was published in December, 2014 in *Science*. We have used these models in Aim 3 to develop effective combinations to overcome the defect in apoptosis which has led to a CTEP-sponsored clinical trial combining AZD9291 and ABT-263.

Our research has expanded beyond just assessing BIM, and is also focusing on the role of a diminished apoptotic response as clones develop resistance to targeted therapies. Although BIM is one such mechanism, it is not the only one. We are now also trying to identify the other mechanisms as well.

Aim 1: Validate BIM as a biomarker that predicts outcome in patients treated with EGFR and ALK inhibitors.
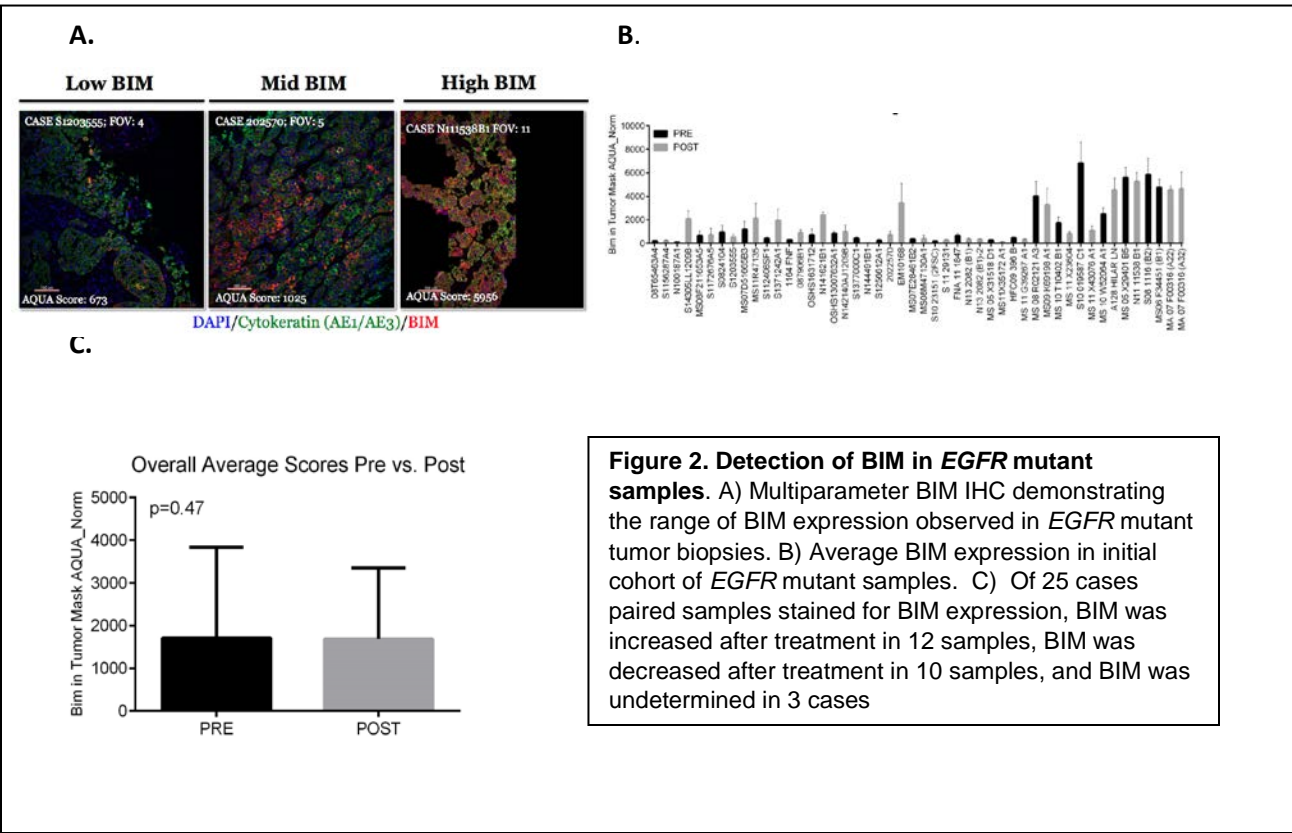
Task 1:

Current objectives: obtain biopsies from 100 *EGFR* mutant lung cancer patients and 60 *ALK*-translocated lung cancer specimens prior to TKI treatment.

Summary of Results, Progress and Accomplishments: Since obtaining this award we have accumulated baseline (pre-treatment) material from >170 *EGFR* mutant lung cancer patients and >100 biopsies from *ALK*-translocated patients prior to therapy (See Tables Below in Aim 2). This has been accomplished through our repeat biopsy program. Therefore, we have already exceeded the number of samples proposed for the entire award. We anticipate obtaining >20 additional tumor specimens from patients prior to 2nd and 3rd generation TKI inhibitor treatment.

Subtasks.

1A. Current objectives: Perform BIM IHC and RNA ISH on approximately 100 pre-treatment *EGFR* mutant lung cancer specimens. These slides will be processed from paraffin-embedded tissue.

Summary of Results, Progress and Accomplishments: We have worked closely with Dr. David Rimm at Yale University to develop a robust, quantitative IHC for the detection of BIM. The assay has been developed and validated using a set of 25 of paired *EGFR* mutant samples. Initial results are shown in Figure 2.

Figure 2. Detection of BIM in *EGFR* mutant samples. A) Multiparameter BIM IHC demonstrating the range of BIM expression observed in *EGFR* mutant tumor biopsies. B) Average BIM expression in initial cohort of *EGFR* mutant samples. C) Of 25 cases paired samples stained for BIM expression, BIM was increased after treatment in 12 samples, BIM was decreased after treatment in 10 samples, and BIM was undetermined in 3 cases

While we were eagerly working to optimize and validate BIM IHC staining on *EGFR* mutant lung specimens to determine if this would lead to the use of BIM as a biomarker to predict response, the results from the EURTAC trial were published in a report this past year (Costa, et. al., Clinical Cancer Research, 2014). This publication reported the BIM mRNA expression levels in 83 pre-treatment tumor samples from *EGFR* mutant lung cancer patients with the goal of assessing BIM as a predictive biomarker of progression-free survival, response rate, and overall survival. Using quantitative-PCR, BIM mRNA was analyzed in 83 specimens. BIM expression was classified as low/intermediate in 53 samples (63.96%) and high in 30 samples (36.14%). Analysis revealed that the PFS for patients with low/intermediate BIM expression treated with erlotinib was 7.2 months, while the PFS for patients with high BIM expression treated with erlotinib was 12.9 months. The response rate to erlotinib in patients with low/intermediate BIM expression was 31.58%, compared to 80% in patients with high BIM expression. The overall survival of patients following erlotinib treatment in low/intermediate BIM expressing-tumor samples was 20.8 months, with high BIM-expressing tumor samples exhibiting 24.5 months. This report suggests BIM expression levels is a predictive biomarker of clinical outcome in the upfront, or pre-treatment, setting for EGFR mutant lung cancer.

With the publication of these data, we will not look to duplicate efforts by assessing BIM expression in our expanded panel of pre-treatment *EGFR* mutant biopsy specimens. We are now interested in assessing BIM expression in specimens from patients prior to them receiving a 2nd or 3rd generation EGFR inhibitor.

1B. Current objectives: Perform BIM IHC and RNA ISH on approximately 60 pre-treatment *ALK*-translocated lung cancer specimens. These slides will be processed from paraffin-embedded tissue.

Summary of Results, Progress and Accomplishments: We have already collected more than 90 ALK lung cancer specimens. We believe it to be worthwhile to continue with the analysis of BIM expression in a panel of pre-treatment tumor specimens taken from *ALK*-mutant lung cancer patients who are going on 2nd generation ALK inhibitors. We will be sending an initial panel of 25 pre-treatment *ALK*-mutant lung cancer specimens to Yale for BIM expression analysis.

1C. Current objectives: Prospectively analyze progression free survival (PFS) in relationship with BIM expression, as determined by IHC and RNA ISH.

Summary of Results, Progress and Accomplishments: As mentioned above, the publication of the EURTAC trial results has performed a prospective analysis on clinical outcome as it relates to BIM expression. We will not be performing a redundant analysis in *EGFR* mutant lung cancer samples. We will pursue efforts of performing a prospective analysis on *ALK* mutant lung cancers to determine if BIM expression is predictive of progression-free survival, response rate, and overall survival in this genetic subset. However, we now know that crizotinib is not a highly potent inhibitor. Therefore, this analysis will be performed on tumor samples from patients that go on to treatment with 2nd and 3rd line ALK inhibitors. We are now focusing on determining if cancers with acquired resistance to first-line targeted therapies will exhibit decreased apoptosis

Aim 2: Determine if BIM expression is lost in cancers that develop resistance to targeted therapies.

Task 2:

Current Objectives: Interrogate approximately 50 *EGFR* mutant lung cancers pre- and post-treated matched specimens that have acquired resistant to TKI and approximately 30 *ALK*-translocated lung cancers pre- and post-treated matched specimens that have acquired resistance to TKI.

Summary of Results, Progress and Accomplishments: Since obtaining this award, we have exceeded our original goal by accumulating matched pre- and post-treatment paired tumor material from 136 *EGFR* mutant lung cancer patients and 78 *ALK*-translocated patients (see Table below). We have also been able to develop cell lines from many of these biopsies. We have determined that BIM expression is lost in a subset of the resistant cancers that are insensitive to subsequent EGFR TKIs.

Pre-EGFR TKI Specimens	Post-EGFR TKI Specimens	Paired Pre-/Post-EGFR TKI Specimens
174	223	136

Pre-ALK TKI Specimens	Post-ALK TKI Specimens	Paired Pre-/Post-ALK TKI Specimens
105	120	78

Subtasks.

2A. Current objectives: Make *EGFR* mutant cell lines resistant to the EGFR TKI gefitinib (cell-lines commercially available from ATCC or acquired from the Center for Molecular Therapeutics at Mass General Hospital Cancer Center).

Summary of Results, Progress and Accomplishments: Please see the Progress Report from Jeff Engelman.

2B. Current objectives: Use commercially available *ALK* translocated cell lines to generate resistant clones to the ALK TKI crizotinib

Summary of Results, Progress and Accomplishments: As mentioned above, we have been very successful in our ability to generate cell lines derived from patient biopsies both before treatment and at the time of resistance (Please see Table below in Subtask 2E). For this reason, we are no longer generating resistance to TKIs in commercially-available cell lines (since there only a few such lines). Moving forward, we will only generate resistance in cell lines derived from patients before treatment or use cell lines derived from patients at the time of resistance.

2C. Current objectives: Determine if BIM levels are reduced in resistant cell lines compared to parental cell lines, and whether resistant lines have a reduced apoptotic response to second-line targeted therapies.

Summary of Results, Progress and Accomplishments: Please see the Progress Report from Jeff Engelman.

2D. Current objectives Make approximately 10 patient-derived resistant cell line models by establishing cell lines from patients with treatment-naïve *EGFR* mutant lung cancers, and exposing them in vitro in increasing concentrations of EGFR TKI

Summary of Results, Progress and Accomplishments: As noted above, we have had great success is establishing cell lines from patient specimens both before treatment and at the time of resistance to therapy. For this reason, we will no longer be generating resistance in pre-treatment patient-derived cell lines. Below is the table of resistant models that we have generated directly from patient biopsies.

Cell Line	Method	Drug	Number of models	Resistance Mechanism(s)
PC9	Increasing Dose	Gefitinib	3	T790M(2), Sustained ERK act. (1)
HCC827	Increasing Dose	Gefitinib	1	MET Amplification
H3255	Increasing Dose	Gefitinib	1	T790M
H1975	Increasing Dose	Dacomitinib	2	EMT
MGH119	Increasing Dose	Gefitinib	1	T790M
MGH119-GR*	Increasing Dose	WZ4002	5	Sustained Akt act., EMT
MGH119-GR*	High Initial Dose	WZ4002	In process	Unknown
MGH119	High Initial Dose	WZ4002	2	Sustained ERK and Akt act.
MGH121	Increasing Dose	WZ4002	5	EGFR C797S (1), Sustained ERK (2), Unknown (2)
MGH134	Increasing Dose	WZ4002	4	Unknown
MGH134	High Initial Dose	WZ4002	5	Unknown
MGH141	Increasing Dose	WZ4002	3	Unknown
MGH164	Increasing Dose	WZ4002	4	EMT
MGH707	High Initial Dose	CO-1686	In process	Unknown

* MGH119-GR is the gefitinib resistant (T790M+) model derived from MGH119 pt

2E. Current objectives: Make approximately 10 patient-derived resistant cell line models by establishing cell lines from patients with treatment-naïve *ALK* translocated lung cancers, and exposing them *in vitro* to increasing concentrations of ALK TKI

Summary of Results, Progress and Accomplishments: As noted above, we have had great success is establishing cell lines from patient specimens both before treatment and at the time of resistance to therapy. For this reason, we will no longer be generating resistance in pre-treatment patient-derived cell lines. Below is the table of resistant models that we have generated directly from patient biopsies.

Patient derived Cell line	Patient relapsed on	Oncogene	ALK genetics	known mechanism of resistance
MGH006-1A	untreated	EML4-ALK Var 1	WT	
MGH026-1A	untreated	EML4-ALK Var 3	WT	
MGH039-1A	untreated	EML4-ALK Var 1	WT	
MGH048-1A	untreated	EML4-ALK Var 1	WT	
MGH064-1B	untreated	EML4-ALK Var 2	WT	
MGH010-1A	Crizotinib	EML4-ALK Var 1	WT	SRC hit
MGH021-2C	Crizotinib	SQSTM1-ALK	G1269A	G1269A
MGH022-2A	Crizotinib	EML4-ALK Var 2	WT	no hit in screen
MGH025-1B	Crizotinib	EML4-ALK Var 1	WT	EGFR, SRC
MGH044-1B	Crizotinib	EML4-ALK Var 2	WT	EGFR, SRC
MGH045-1B	Crizotinib	EML4-ALK Var 1	L1196M	L1196M+EGFR, SRC
MGH045-2A	Crizotinib	EML4-ALK Var 1	L1196M 50%	
MGH051-1B	Crizotinib	EML4-ALK Var 3	WT	
MGH065-1C	Crizotinib	EML4-ALK Var 1	WT	
MGH065-1B	Crizotinib	EML4-ALK Var 1	WT	
MGH073-2B	Crizotinib	EML4-ALK Var 3	WT	
MGH075-3D	Crizotinib	EML4-ALK Var 2	WT	
MGH021-5A	LDK	SQSTM1-ALK	G1202R	G1202R
MGH034-2A	LDK	EML4-ALK Var 5	WT	MEK activating mutation
MGH049-1A	LDK	EML4-ALK Var 1	WT	EGFR, SRC
MGH023-2A	LDK	EML4-ALK Var 1	F1174C	F1174C
MGH051-2C	LDK	EML4-ALK Var 3	G1202R	
MGH089-1	LDK	EML4-ALK Var 1	WT	
MGH092-1	LDK	EML4-ALK Var 1	G1202del	
MGH075-2E	LDK	EML4-ALK Var 2	WT	
MGH056-1G	Alectinib	EML4-ALK Var 1	I1171T	I1171T
MGH084-1D	Criz/Alectinib/LDK		I1171N, C1156Y	

2F. Current objectives: Determine if patient-derived cell lines collected at time of progression on first-line therapy have varying degrees of apoptotic response to 2nd and 3rd generation EGFR or ALK inhibitors.

Summary of Results, Progress and Accomplishments: As noted above, we have had great success at generating cell lines derived directly from patients at the time of progression. There are now several new EGFR and ALK inhibitors that can overcome resistance to 1st generation EGFR and ALK inhibitors. We have been using these aforementioned cell lines to determine if a subset of these resistant cancers has a diminished apoptotic response to 2nd and 3rd generation

inhibitors. Indeed, we have found this to be the case and this observation has led to a novel therapeutic approach described in Aim 3.

2G. Current objectives: Determine if any of these acquired resistant cell line models and patient-derived resistant models have common, already identified major resistant mechanisms (such as EGFR *T790M*) and whether they have a depressed apoptotic response to second-line targeted therapies.

Summary of Results, Progress and Accomplishments: Please see the Progress Report from Jeff Engelman.

2H. Current objectives: In acquired resistant models that do not have common major resistant mechanisms, determine if low BIM is a primary major resistant mechanism.

Summary of Results, Progress and Accomplishments: Please see the Progress Report from Jeff Engelman.
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2I. Current objectives: To expand our studies of the role of EMT and BIM in apoptotic response, we propose to look at the expression of both BIM and EMT markers in a larger panel of *EGFR* mutant patient-derived cell lines resistant to first-line TKI therapy.

Summary of Results, Progress and Accomplishments: Please see the Progress Report from Jeff Engelman.

Aim 3: Assess novel therapeutic strategies for cancers with low BIM expression that aim to increase BIM and thereby enhance response.

Task 3:

Current Objectives: Interrogate 200 female NU/NU mice for this task.

Summary of Results, Progress and Accomplishments: Please see below in section on Subtasks.

Subtasks.

3A. Current objectives: Determine if demethylase inhibitors increase free BIM and if co-treatment with demethylase inhibitors and TKIs re-sensitize low BIM expressing resistant cancers, identified previously and in Aim 2, to apoptosis in vitro.

Summary of Results, Progress and Accomplishments: These studies have not yet been initiated. We have focused significant efforts for objective 3D. Those results have been very impressive, leading to a clinical trial sponsored by CTEP and they have occupied more effort than we initially planned.

3B. Current objectives: Determine whether there are alterations at the BIM promoter causing epigenetic silencing at the BIM locus in resistant lung cancer models identified previously and in Aim 2.

Summary of Results, Progress and Accomplishments: Please see the Progress Report from Jeff Engelman.

3C. Current objectives: Determine whether agents that work by reversal of epigenetic silencing (e.g.demethylase inhibitors) lead to de-repression of BIM in these cancers.

Summary of Results, Progress and Accomplishments: Please see the Progress Report from Jeff Engelman.

3D. Current objectives: Determine whether the amount of free BIM can be maximized in low BIM expressing resistant cancer models identified previously and Aim 2, by addition of ABT-263, through immunoprecipitation analysis of Bcl-2 family member proteins.

Summary of Results, Progress and Accomplishments: We have determined that free BIM can be enhanced by addition of ABT-263.

3E. Current objectives: Determine whether BH3 mimetics sensitize low BIM expressing lung cancers identified previously and Aim 2 to TKIs to apoptosis.

Summary of Results, Progress and Accomplishments: Please see the Progress Report from Jeff Engelman.

3F. Current objectives: Use the pharmaceutical strategy that does in fact re-sensitize low BIM expressing cancers to TKIs, and treat these cancers with this combination in vivo by xenografting female NU/NU mice.

Summary of Results, Progress and Accomplishments: As described in Jeff Engelman's progress report, we have tested the combination of ABT263 + WZ4002 in xenograft models of in vitro acquired resistance (PC9) as well as in a patient-derived cell line from resistant tumor (MGH134) and demonstrated that this combination induces dramatic tumor regressions (see Figure 9 in Jeff Engelman's progress report).

4.KEY RESEARCH ACCOMPLISHMENTS:

- During this year, we have continued to surpass our initial goals of obtaining pre-treatment and post-treatment biopsy specimens for both *EGFR* mutant and *ALK*-translocated tumors.
- We have successfully optimized our methods to establish cell lines taken from patient-derived tumors taken at the time of progression. This has allowed us to expand the number of both in vitro and xenograft models for laboratory use.
- Intrinsic loss of apoptotic response appears to be a distinct mechanism contributing to acquired resistance and not mutually exclusive with commonly clinically observed genetic clinical mechanisms of resistance such as T790M (manuscript under review).

- Cancers that evolve from drug tolerant persisters likely maintain an apoptotic defect when they subsequently genetic mutations leading to resistance (manuscript under review).
- Cancers with T790M and suppression of apoptotic response may be less sensitive to subsequent therapy with next generation irreversible EGFR inhibitors
- Cancers with loss of apoptotic response can be resensitized to TKI treatment by use of BH3 mimetics
- **New clinical trial combining ABT263 with AZD9291 is opening based on these results**

5.CONCLUSION:

We have established that a subset of resistant cancers that developed T790M have decreased apoptotic response to irreversible EGFR inhibitors in vitro and in vivo. The changes in these cells that underlie the loss of apoptotic response may involve BIM in some cases but overall appears to be more complex. We have determined that the combination of BH3 mimetics plus irreversible EGFR inhibitors is effective against many of these cancers in preclinical studies. These data have provided rationale for planned upcoming clinical trials investigating the combination of navitoclax (ABT263) with irreversible EGFR inhibitors.

6.PUBLICATIONS, ABSTRACTS, AND PRESENTATIONS:

Two manuscripts describing this data have been written:

"Dynamic evolution of resistance to EGFR blockade from drug tolerant cancer cells"

-Under review at *Nature Medicine*

"Epithelial-mesenchymal transition antagonizes EGFR inhibitors in *EGFR* mutant NSCLCs by suppressing BIM"

7.INVENTIONS, PATENTS AND LICENSES: Nothing to Report

8.REPORTABLE OUTCOMES:

Two manuscripts describing the combination of ABT263 and irreversible EGFR inhibitors have been written. One is under review at *Nature Medicine* and one will be submitted. These data are the basis of an upcoming clinical trial

9.OTHER ACHIEVEMENTS: Nothing to Report

10.REFERENCES: Nothing to Report

11.APPENDICES: Nothing to Report